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(54) A separation device for magnetisable particles

(57) A magnetic separation device comprises a 96-well microplate 5 and a transparent base plate 1 (Figure 2) to which a number of magnets 2 are affixed, the base plate 1 fitting onto the base of the microplate 5 (Figure 3) with the magnets symmetrically arrayed such that each magnet is surrounded by four wells 6 of the microplate. The device is used for separating magnetisable particles provided with a coating for selective affinity for one or more compounds to be removed from the liquid in which the particles are suspended. The device causes the particles to be attracted to one side of a well for analysis to be made by a photometric, fluorometric or luminometric microplate reader.

Fig. 4

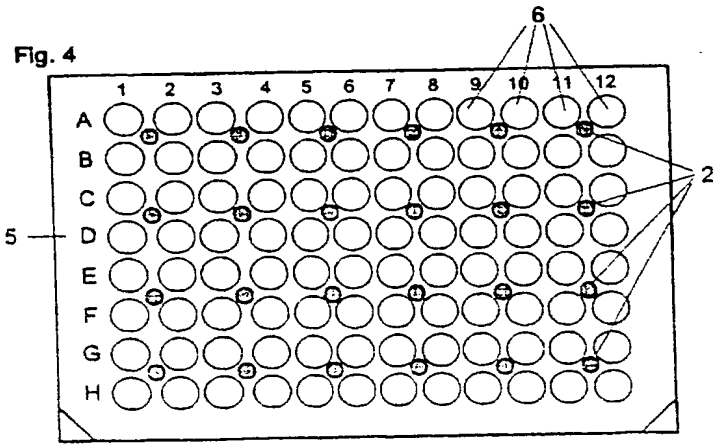

Fig. 6

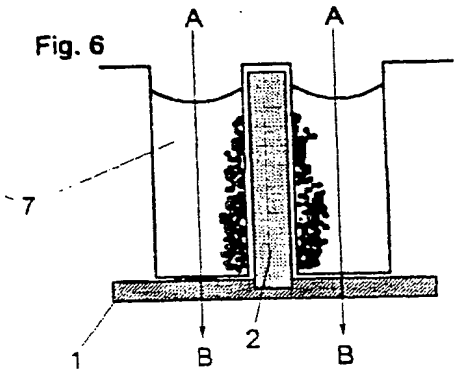

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Fig. 1

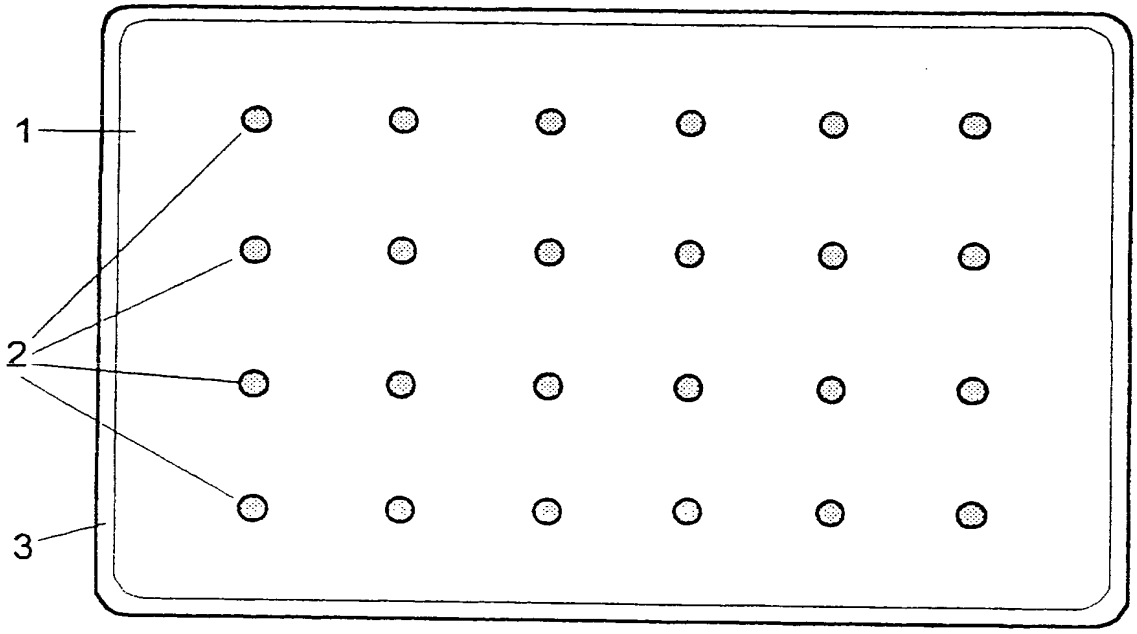


Fig. 2

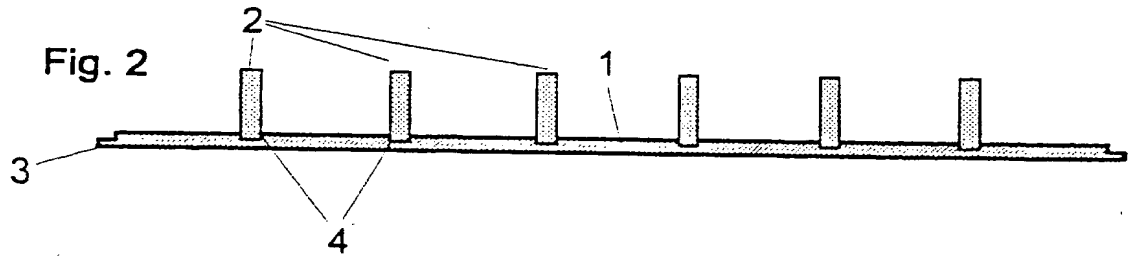


Fig. 3

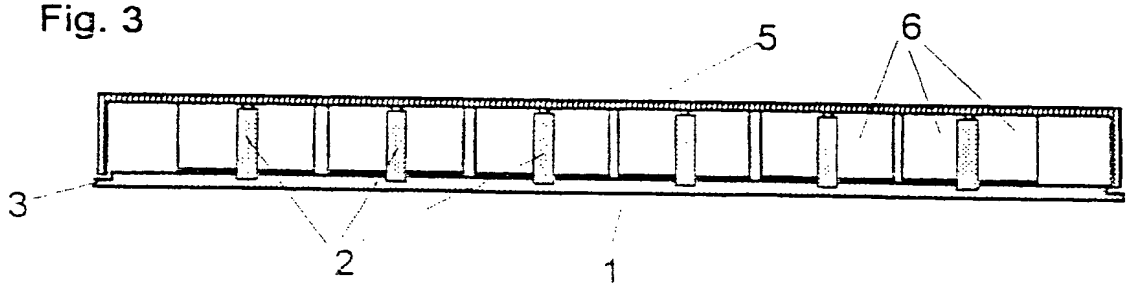


Fig. 4

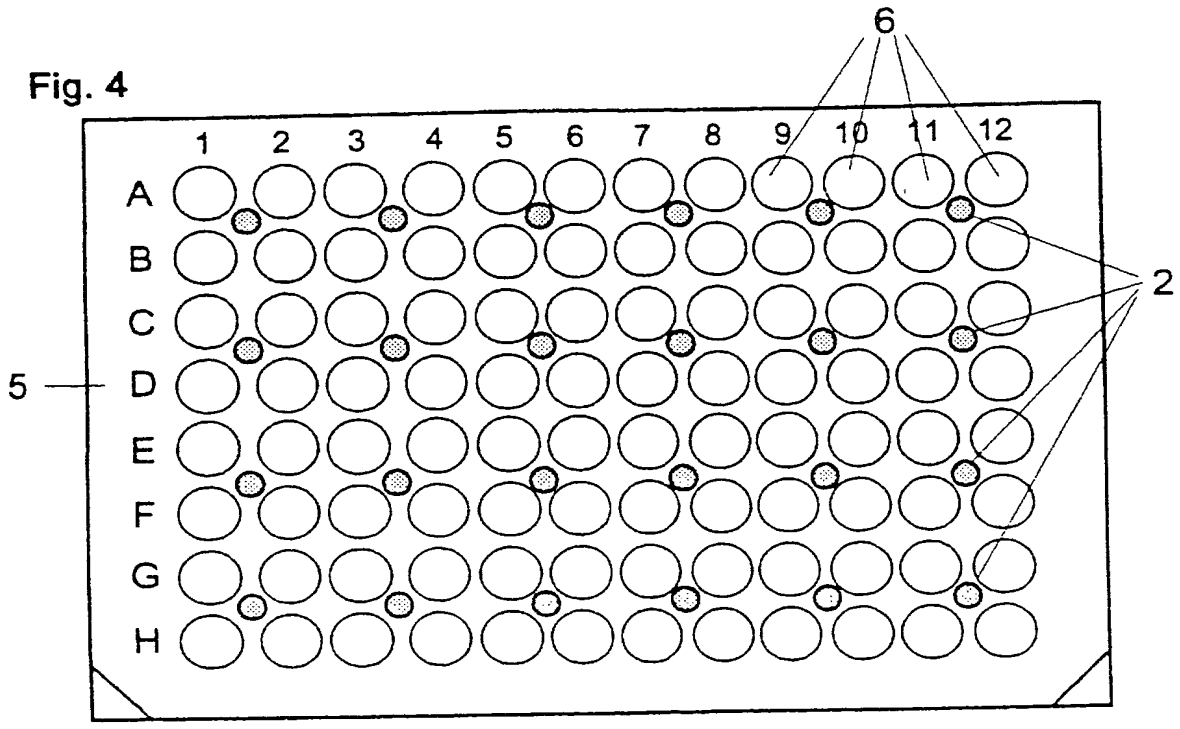


Fig. 5

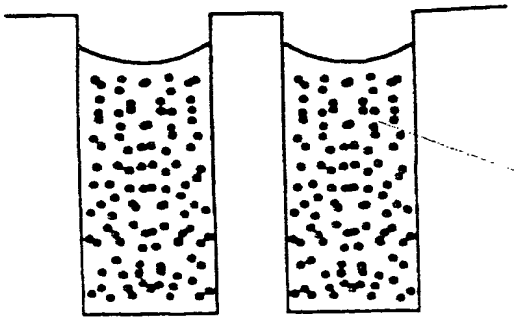
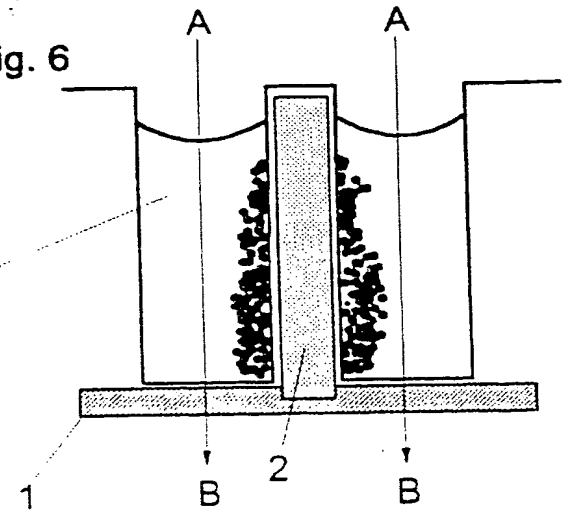


Fig. 6



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SEPARATION DEVICE FOR MAGNETISABLE PARTICLES

This invention relates to a separation device for magnetisable particles.

DESCRIPTION

In the fields of biochemistry, molecular genetics, cell, organelle and virus separation, environmental analysis and medical diagnostics the use of magnetic attraction is becoming widespread and increasingly accepted as a simple and rapid small-scale separation method with a number of advantages compared with other methods such as the use of columns or centrifugation. These magnetic methods usually take the form of the use of magnetic particles coated with a reactive substance which has an affinity for certain proteins, cells, virus particles, pesticides, environmental contaminants or other materials which it is desired to analyse. Thus, when a suspension containing the magnetic carrier particles is added to the analyte, the component for which the particles have affinity is bound to the said particles and can then be separated from the rest of the suspension by means of suitable magnets. Such reactive substances which can be used in this way often have remarkable avidity and specificity for certain compounds, examples of which are antibodies (immunoglobulins) and oligonucleotides. The assays performed for the target compound present in the sample are effected by reactions using a labelled reagent, the assay being performed by measuring the amount of label either bound to the solid phase or unbound in solution.

An additional advance in this field of analysis is the ability to be able to analyse much smaller samples than could be used with earlier technology. A corollary of this has been the widespread use of methods which use and handle large numbers of small samples and which lend themselves to automation, an example of which has been the widespread adoption of standardised 96-well microplates such as Microtitre® plates for such analyses. These plates permit the near simultaneous photometric, fluorometric or luminometric analysis of all 96 samples containing as little as 50 µl of solution in a few seconds when used in conjunction with suitable electronic microplate readers.

Although existing apparatuses are known for the simultaneous performing of multiple magnetic separations in a plurality of containers for heterogeneous assays, the known methods have limitations of scale or problems of adaptability to microtitre type assays. In particular, the devices already described either use sample tubes containing 1 ml or greater or, if designed for use with 96-well microplates such as Microtitre® plates or Micronic® type tubes are not adaptable for the simultaneous analysis of samples and the separation of magnetisable particles. It would be a tremendous advantage in convenience, accuracy and time if such analyses could be performed in the same sample container as is used to effect the magnetic separation. The present invention describes a means by which such magnetic separation may be effected and the analysis performed without the transfer of liquid samples contained in 96-well microplates.

A specific example of the invention will now be described with reference to the accompanying figures in which:-

Fig, 1 shows the device in plan view.

Fig. 2 shows the device in horizontal section.

Fig. 3 shows the device as in Fig. 2 but when placed against the base of a microplate.

Fig. 4 shows the layout of the magnets contained within the device relative to the sample wells of a microplate.

Fig. 5 and Fig. 6 show the principle of operation of the device.

Referring to the drawings, the separation device consists of base plate 1 made of clear transparent plastic cut and rebated to form a flange 3 to enable it to fit on or in the base of a 96-well microplate and drilled with holes 4 to accommodate magnets 2, Fig. 1. The magnets 2 are cut or cast to fit the holes 4 in the base plate and of such a size that they will fit in the spaces between the wells of the microplate. The magnets are optimally high intensity magnets such as those made of Neodymium/Iron/Boron or Samarium/Cobalt. These magnets would typically be between 1 and 4 mm in diameter or square and 1 and 12 mm in length. Optimally, the upper edge of each magnet is chamfered or radiused to improve location of the magnets within the recesses between the microplate wells. The magnets are attached in the recesses of the base plate by a suitable adhesive and in conjunction with the base plate constitute the invention. Alternatively, the plastic base plate may be cast directly around the array of magnets. The magnets are optimally placed in an array so that each magnet is surrounded by four microplate wells. The illustration, Fig. 4 shows the preferred configuration of the device such that each magnet in the device is surrounded by four receiving wells or orifices 6 in the plate 5 and thus has a total of 24 magnets. Alternative geometries are also possible such that more magnets may be evenly arrayed between the receiving wells but surprisingly, such geometries were not found to aid significantly the separation of the magnetisable particles. The base plate 1 is machined of such dimensions that it recesses into the base of the microplate and contributes minimally to the total thickness when the device is placed on the plate, although the presence of the thin flange 3 enables the convenient disassembly of the device from the microplate. This arrangement is shown in Fig. 3 and contributes a particular advantage so that the device being thin, transparent and flat that, when placed on the microplate enables the plate to be inserted in a suitable photometric microplate reader. Such a principle is shown in Fig. 5 and Fig. 6. Fig. 5 shows a suspension of magnetisable particles or microspheres 7 contained within the receiving orifices or wells of a microplate. Fig. 6 shows the same microplate with the magnetisable device in place. It can thus be seen that the magnetisable particles are drawn to one side, allowing the light beam A→B produced by the photometric microplate reader to pass unimpeded through the solution. Such principles are well known as the basis of methods by which light-absorbing or emitting materials may be quantified when in solution by spectrophotometric, spectrofluorometric or luminometric means and its use in conjunction with the claimed device and magnetisable particles represents a peculiar advantage over other devices previously claimed.

CLAIMS

A SEPARATION DEVICE FOR MAGNETISABLE PARTICLES

1 A magnetic device for separating magnetisable particles provided with a coating for selective affinity for the compounds to be removed for the suspension solution consisting of (a) a base means consisting of a sheet of clear, transparent flat plastic (1) adapted to fit in or on the base of a 96-well microplate (5) adapted in turn to contain the magnetisable particles or microspheres (b) a plurality of magnet means (2) attached to the base means and spaced equidistantly around the edge of each microplate well (6) and as substantially described herein with reference to Figs. 1-6 of the accompanying drawings.

2 A magnetic separation device according to claim 1 such that each magnet means is surrounded by four microplate wells (6).

3 A magnetic separation device according to claims 1 to 2 whereby the base means is rebated to form a flange (3) to fit the base of a 96-well microplate such that when attached, the total thickness of the microplate is increased by no more than 4 mm.

4 A magnetic separation device according to claims 1 to 3 in which, when attached to a 96-well microplate, the microplate together with the device may be inserted into and the solution contained therein may be analysed by a photometric, fluorometric or luminometric microplate reader.

5 A magnetic separation device as claimed in claims 1 to 4 in which the magnet means (2) are attached to the base means by means of press fitting into suitably sized holes (4) impressed, machined or drilled into the base means (1).

6 A magnetic separation device as claimed in claims 1 to 5 in which the magnet means (2) are fixed into the holes (4) by the use of an adhesive.

7 A magnetic separation device as claimed in claims 1 to 6 in which the base means (1) is constructed by means of injection moulding around the magnet means (2).

8 A magnetic separation device as claimed in claims 1 to 7 in which the magnet means (2) are constructed of Iron.

9 A magnetic separation device as claimed in claims 1 to 8 in which the magnet means (2) are constructed of Samarium and Cobalt.

10 A magnetic separation device as claimed in claims 1 to 9 in which the magnet means (2) are constructed of Iron, Neodymium and Boron.

11 A magnetic separation device as claimed in claims 1 to 10 in which the upper surfaces of the magnet means (2) are chamfered or radiused.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report)	Application number GB 9508726.8
Relevant Technical Fields (i) UK Cl (Ed.N) B1X; G1B (ii) Int Cl (Ed.6) B01L (3/00)	Search Examiner MR J L FREEMAN Date of completion of Search 3 NOVEMBER 1995
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE: EDOC, WPI	Documents considered relevant following a search in respect of Claims :- 1 TO 11

Categories of documents

X: Document indicating lack of novelty or of inventive step.

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A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
X	EP 0317286 A	(GENE-TRAK SYSTEMS) Figures 1 to 3	1
X	EP 0030086 A	(TECHNICON INSTRUMENTS) Figure 3	1
X	WO 93/05443 A	(MEDICAL RESEARCH COUNCIL) Figures 3 to 5	1

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